

Surfactants in the management of rhinopathologies

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ABSTRACT

Background: Surfactants are a class of amphiphilic surface active compounds that show several unique physical properties at liquid–liquid or liquid–solid surface interfaces including the ability to increase the solubility of substances, lower the surface tension of a liquid, and decrease friction between two mediums. Because of these unique physical properties several *in vitro*, *ex vivo*, and human trials have examined the role of surfactants as stand-alone or adjunct therapy in recalcitrant chronic rhinosinusitis (CRS).

Methods: A review of the literature was performed.

Results: The data from three different surfactants have been examined in this review: citric acid zwitterionic surfactant (CAZS; Medtronic ENT, Jacksonville FL), Johnson's Baby Shampoo (Johnson & Johnson, New Brunswick NJ), and SinuSurf (NeilMed Pharmaceuticals, Santa Rosa, CA). Dilute surfactant therapy shows *in vitro* antimicrobial effects with modest inhibition of bacterial biofilm formation. In patients with CRS, surfactants may improve symptoms, most likely through its mucolytic effects. In addition, surfactants have several distinct potential benefits including their ability to improve an irrigant's penetration of the nonoperated sinus and their synergistic effects with antibiotics. However, surfactants potential for nasal irritation and possible transient ciliotoxicity may limit their use.

Conclusion: Recent data suggest a possible therapeutic role of surfactants in treating rhinopathologies associated with mucostasis. Further investigation, including a standardization of surfactant formulations, is warranted to further elucidate the potential benefits and drawbacks of this therapy.

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The word “surfactant” is derived from surface active agent. Surfactants are a category of compounds that show amphipathic properties, containing both hydrophobic and hydrophilic characteristics, which allow the compound to be solvent in both water and organic substrates.¹ When used as an additive, surfactants can increase the solubility and subsequent biodegradation of additional hydrophobic or insoluble organic compounds.¹ In addition, endogenous surfactants in the respiratory system act to decrease the surface tension and viscosity of airway mucus, increasing the efficiency of energy transfer from the cilia to the mucus layer.² Of note, soaps and shampoos, used by consumers as wetting and degreasing agents, are common examples of surfactants.

BIOFILMS

Bacterial biofilms consist of a complex, organized community of microorganisms, which anchor to both biotic and abiotic surfaces and are contained and protected by a self-produced extracellular polymeric substance (EPS).³ The EPS makes the bacterial biofilm 100–1000 times more resistant to antibiotic treatment than planktonic (suspended, without EPS) bacteria.⁴ A subset of patients with recalcitrant chronic rhinosinusitis (CRS), despite appropriate medical and surgical management, have been found to harbor bacterial biofilms within the sinonasal mucosa.^{5,6} The most common bacterial species found in CRS after endoscopic sinus surgery include *Staphylococcus aureus* and *Pseudomonas aeruginosa*.⁷

Previous animal models have shown the limited effectiveness of existing topical therapies against bacterial biofilms.^{8,9} In rabbit maxillary sinuses inoculated with *P. aeruginosa*, topical tobramycin resulted in a dose dependent eradication of planktonic *P. aeruginosa*

within the lumen of the sinus but did not eradicate bacterial biofilms attached to the mucosa. Furthermore, histological examination of the tobramycin-treated tissue showed improvement in degree of infection but persistent inflammation within the mucosa and underlying bone.⁸

RATIONALE FOR SURFACTANT USE IN RECALCITRANT CRS

Several studies have implicated sinonasal bacterial biofilms as a source of persistent symptoms in patients with recalcitrant CRS despite appropriate therapeutic intervention.^{5–10} Thus, therapies directed at removing mucosal biofilms were developed. Based on prior work in the orthopedic literature showing efficacy of surfactants, but not antibiotics, in removing bacteria from stainless steel screws,¹¹ several investigations were published reporting on surfactant-based CRS therapies. The topical use of surfactants for CRS has two potential benefits, as a biocide with activity against planktonic and biofilm-associated microbes and as a mucoactive agent to decrease mucus viscosity.¹² The data from three different surfactants have been examined in this review (Table 1): citric acid zwitterionic surfactant (CAZS; Medtronic ENT, Jacksonville FL), Johnson's Baby Shampoo (Johnson & Johnson, New Brunswick NJ), and SinuSurf (NeilMed Pharmaceuticals, Santa Rosa, CA).

CAZS: IN VITRO AND EX VIVO ANIMAL MODELS

Biofilm resistance to eradication is partly attributable to the EPS calcium–ion bridges that produce gelling or “cross-links” that greatly strengthen the physical structure of the biofilm, thus aiding in resisting degradation.¹³ In conjunction with a cation chelating agent that would disrupt the bridging, a surfactant would be able to solubilize much of the EPS polymer, which could then be removed with power irrigation.¹³ This approach was investigated by Desrosiers *et al.* They used a combination of citric acid and caprylyl sulfobetaine, a zwitterionic surfactant.¹³ The citric acid acts to chelate the calcium in the calcium–ion bridges, while the surfactant brings the detached chains into solution. In their *in vitro* study, bacterial isolates of *S. aureus* and *P. aeruginosa* from patients with refractory CRS were grown in drip chambers to form a biofilm. Eradication of the biofilm was attempted with static administration of CAZS, hydrodynamic administration of CAZS (sprayed using a pressurized jet lavage), and hydrodynamic administration of saline. Although all treatment arms led to signifi-

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Table 1 Recent Surfactant Investigations

Study	Surfactant	Method	Conclusion(s)
Desrosiers <i>et al.</i> (2007) ¹³	CAZS	<i>In vitro</i> (evaluating for antibiofilm effects)	Both static and hydrodynamic administration of CAZS disrupt <i>Staphylococcus aureus</i> and <i>Pseudomonas aeruginosa</i> biofilms
Le <i>et al.</i> (2008) ¹⁶	CAZS	<i>In vivo</i> , sheep (evaluating for antimicrobial effects)	One-time CAZS administration initially reduced <i>S. aureus</i> biofilm size, but there was robust biofilm regrowth at day 8 post-CAZS
Tamashiro <i>et al.</i> (2009) ¹⁴	CAZS	<i>In vivo</i> , rabbit (evaluating for ciliotoxicity)	CAZS administration leads to denudation of cilia with near complete recovery by day 6 CAZS administration is associated with initial blunting of CBF with near complete recovery by day 6
Valentine <i>et al.</i> (2011) ¹⁷	CAZS	<i>In vivo</i> , sheep (evaluating for effect on cilia morphology)	Visual worsening of cilia morphology, but did not evaluate the effect on CBF
Chiu <i>et al.</i> (2008) ¹⁸	1% Johnson's Baby Shampoo	<i>In vitro</i> (evaluating antibiofilm effects) Human prospective trial, 18 recalcitrant CRS patients (open-label, nonrandomized, and noncontrolled)	Inhibited <i>P. aeruginosa</i> biofilm formation Forty-seven percent of subjects reported overall improvement in subjective symptoms Sixty percent reported decreased mucus thickness Fifty-three percent reported decreased postnasal drainage
Issacs <i>et al.</i> (2011) ²¹	1% Johnson's Baby Shampoo	Human blinded trial of 27 healthy volunteers (evaluating for mucociliary)	Increase in mucociliary clearance time after baby shampoo administration but there was not a control group
Farag <i>et al.</i> (2012) ²⁰	1% Johnson's Baby Shampoo	Human randomized controlled trial of 44 CRS subjects, immediate postoperative use of baby shampoo vs control (hypertonic saline)	Both baby shampoo and control groups showed significant improvement in symptoms over time and olfactory testing; however, there was no statistical difference between the two groups Baby shampoo group reported higher rate of side effects (nasal burning and headache) and study discontinuation
Chiu <i>et al.</i> (2011) ¹²	SinuSurf	Sinonasal mucosal explants and primary sinonasal epithelial cultures	SinuSurf did not show any acute ciliotoxicity nor change in ciliary beat frequency
Kofonow <i>et al.</i> (2012) ²⁵	SinuSurf	<i>In vitro</i> (evaluating for antimicrobial effects)	Daily flushing of sinus irrigation bottles with SinuSurf reduced bacterial load Addition of SinuSurf to an antibiotic solution eradicated bacteria at lower antibiotic concentrations than when using antibiotics alone
Rohrer <i>et al.</i> (2012) ²²	SinuSurf	Cadaver study	SinuSurf decreased surface tension of irrigation solution SinuSurf improved irrigant penetration into nonoperated sinuses

CAZS = citric acid zwitterionic surfactant; CRS = chronic rhinosinusitis; CBF = ciliary beat frequency.

cant reductions in bacterial counts, hydrodynamic CAZS was found to be the most effective, leading to a 99.9% reduction in colony-forming unit (CFU) counts. Confocal scanning laser microscopy confirmed a massive reduction in the size and order of the remaining biofilm.

After the *in vitro* success of CAZS against biofilms, two preclinical animal studies were undertaken, one evaluating toxicity and the other evaluating efficacy. Tamashiro *et al.* studied the *in vivo* cilia effects of CAZS on a rabbit model to assess safety of CAZS as a therapeutic agent.¹⁴ Investigators surgically inserted indwelling maxillary sinus irrigation catheters into 20 New Zealand white rabbits in a manner previously described.¹⁵ After 3 days of healing, the indwelling catheters were irrigated with a one-time 10-mL infusion of the test CAZS solution or normal saline. The rabbits were then killed at 1, 3, or 6 days after the CAZS/control infusion and the sinus mucosa was harvested. The health of the cilia was evaluated by visually assessing the morphological integrity of the cilia with a scanning electron microscope and measuring the explant's ciliary beat frequency (CBF). Assessing the cilia morphology, the results showed an initial denudation of cilia on day 1, but by 6 days after treatment, near complete reciliation was evident.¹⁴ Assessing the physiology, the CBF was initially blunted at days 1 and 3, but there was evidence of recovery

by day 6.¹⁴ In total, the study indicated a reversible ciliotoxic effect of CAZS, but by 6 days after infusion, the epithelium had near complete recovery, showing evidence of reciliation and normalizing CBF.

To assess the *ex vivo* antibiofilm efficacy of CAZS, Le *et al.* examined the impact of CAZS on biofilms in a sheep model of rhinosinusitis.¹⁶ Using endoscopic sinus surgery, investigators inoculated 54 sheep frontal sinuses with *S. aureus*. After 8 days of bacterial inoculation, each frontal sinus was randomized to a control or one of several treatments. After receiving the treatments and then waiting a predetermined number of days, the sheep were killed and the sinus mucosa were harvested and analyzed with confocal scanning laser microscopy and image analysis software to assess the percent of total surface area that was covered by biofilm. In the control sinuses, receiving no treatments or flushes, 31.7% of total surface area was covered by biofilm. CAZS, delivered intraoperatively in a pulsatile fashion with a hydrodebrider endoscopic sinus irrigation system (Xomed Hydrodebrider; Medtronic), showed 6.6% biofilm coverage 1 day posttreatment, but 21.95% biofilm coverage 8 days posttreatment. The higher amount of biofilm coverage at day 8 suggests a possible regeneration of the biofilm in the absence of continuous CAZS treatments.

In the investigators' similar follow-up study, they again inves-

tigated the antibiofilm activity of CAZS (with or without the use of a hydrodebrider) but added an additional assessment of cilia morphology.¹⁷ The CAZS-exposed mucosa was extracted and viewed with an electron microscope, which showed a visual worsening of the cilia morphology. However, the investigators did not analyze the CBF of the CAZS-exposed mucosa, which limits the ability to correlate the changes in ciliary morphology with ciliary function.

JOHNSON'S BABY SHAMPOO THERAPY IN RECALCITRANT POSTSURGICAL CRS PATIENTS

In addition to CAZS, studies have examined the potential therapeutic role of a readily available surfactant, Johnson's Baby Shampoo, which is a popular consumer product used to wash away grease from hair. Its active ingredients include three chemical surfactants: PEG-80 sorbitan laurate, cocamidopropyl betaine, and sodium trideceth sulfate. Because of Johnson's Baby Shampoo's long record of consumer safety and its known surfactant ingredients, Chiu *et al.* examined the *in vitro* and human *in vivo* bactericidal and mucolytic effects of Johnson's Baby Shampoo as an adjunctive therapy for CRS.¹⁸ Multiple concentrations of Johnson's Baby Shampoo diluted in isotonic saline were evaluated, and 1% Johnson's Baby Shampoo was found to both inhibit *in vitro* formation of *P. aeruginosa* biofilms and kill planktonic *P. aeruginosa*. Based on this *in vitro* data, the investigators transitioned to a human open-label, nonrandomized, noncontrolled prospective trial, enrolling 18 subjects with recalcitrant CRS despite appropriate medical and surgical intervention (average, 2.8 previous functional endoscopic sinus surgery [FESS] operations; range, 1–6).¹⁸ All patients recruited were at least 3 months after their most recent surgery and had already been irrigating with saline. Subjects were instructed to irrigate with 1% Johnson's Baby Shampoo, 60 mL on each side, twice daily for 4 weeks. Subjects continued to receive their other existing medical management (including nasal steroid spray and, if appropriate, systemic antibiotics or steroids). The Johnson's Baby Shampoo was well tolerated by most subjects, but two subjects dropped out of the study, one because of nasal irritation and the other because of perinasal rash (cocamidopropyl is a known potential allergen),¹⁹ which resolved with discontinuation of the Johnson's Baby Shampoo. One additional subject was lost to follow-up. Overall, 7 of the remaining 15 subjects (46.6%) reported overall improvement in their subjective CRS symptoms, as indicated by their 22-item Sino-Nasal Outcome Test (SNOT-22) with an average decrease of 11.1.¹⁸ Within the SNOT-22, the subdivisions of greatest improvement included improvement in mucus thickness (60% of 15 remaining subjects) and reduction in postnasal drainage (53.3% of remaining subjects), suggesting that Johnson's Baby Shampoo may have therapeutic potential as a mucolytic agent. None of the seven patients who showed symptom improvement received a concomitant course of oral prednisone, but four of the seven patients who showed improvement did receive a course of antibiotics at the time of the study enrollment. In addition to studying symptom resolution, authors evaluated pre- and post-treatment smell testing in 11 of the subjects. Of those 11, 7 (63.6%) had objective improvement on their University of Pennsylvania Smell Identification Test.¹⁸

JOHNSON'S BABY SHAMPOO THERAPY IN EARLY POSTOPERATIVE FESS PATIENTS

Although Chiu *et al.* examined the role of Johnson's Baby Shampoo in recalcitrant CRS patients who remained symptomatic despite appropriate medical and surgical therapy, Farag *et al.* specifically studied the effects of a 1% Johnson's Baby Shampoo solution in the early FESS postoperative period.²⁰ Forty-four adult subjects with CRS were enrolled into the study at their preoperative visit and were prospectively randomized into two different irrigation groups: 1% Johnson's Baby Shampoo (the surfactant group) and hypertonic saline (the

control group). Patients completed objective olfactory testing (phenylethyl alcohol) as well as quality-of-life questionnaires (SNOT-22 and 31-item RSOM-31 Rhinosinusitis Outcome Measure) both preoperatively and over 3 postoperative visits in a 4-month period. Quality-of-life scores significantly improved over time in both irrigation groups, but no statistical difference was seen between the surfactant and the hypertonic saline groups. Olfactory testing significantly improved in both groups 3–4 months after surgery, but there was no significant difference between the two groups. Although quality of life and olfactory results were similar, the surfactant group had a significantly higher rate of side effects and a higher rate of study discontinuation compared with the hypertonic saline group. Fifty-two percent of surfactant group subjects reported side effects (compared with 5% of hypertonic saline subjects) and 20% of the surfactant group of subjects withdrew from the study, whereas none of the hypertonic saline users did. The most commonly reported surfactant group side effects included nasal burning and headache. Patients in the surfactant group additionally complained of the taste of the shampoo and the presence of bubbles in the back of their nose and throat. Ultimately, the trial concluded that surfactant irrigations in the immediate postoperative period, compared with hypertonic saline users, had no impact on quality-of-life scores or olfaction, but was associated with a higher rate of side effects.

JOHNSON'S BABY SHAMPOO AND SINUSURF'S EFFECT ON MUCOCILIARY CLEARANCE

Issacs *et al.* performed an *in vivo* study using saccharine transit time to evaluate the effects of surfactant therapy on mucociliary transport (MCT).²¹ In 27 healthy volunteers (CRS patients were excluded), saccharin was placed on the anterior surface of the inferior turbinate and subjects were told to report when they first tasted the saccharin (mean was 12.09 minutes \pm 4.83). The subjects then irrigated with 50 mL of 1% Johnson's Baby Shampoo, waited 15 minutes, and then the MCT test was repeated (mean was 15.45 \pm 7.71 minutes). The mean difference of 3.37 minutes was statistically significant ($p = 0.031$). Although the results did show an increase in mucociliary clearance time after using the surfactant irrigation, the study did not use a saline control group, limiting the interpretation of the surfactant-specific effect on MCT.

Chiu *et al.* examined the effect of NeilMed's SinuSurf, a novel surfactant solution specifically designed for nasal irrigation, on ciliary function.¹² Investigators added SinuSurf solution to sinonasal mucosal explants as well as primary sinonasal respiratory epithelial cultures and recorded its effect on CBF over a 15-minute period. The measurements showed that the addition of surfactant resulted in no change of CBF with no evidence of respiratory epithelial toxicity.

SINUSURF'S EFFECT ON SINUS PENETRATION OF SINONASAL IRRIGATION FLUID

As mentioned previously, surfactants reduce a liquid's surface tension.¹ Thus, Rohrer *et al.* proposed that adding a surfactant to a sinonasal irrigation solution would lower the irrigation fluid's surface tension, which should increase ostial penetration of the solution.²² The investigators tested this theory by irrigating various solutions (water + dye versus water + dye + surfactant) into five undiseased and undissected cadaver heads, which were prepared by creating sinus burr holes to enable intrasinus visualization during douching. The results indicated that the addition of SinuSurf to the irrigant solution improved sinus penetration compared with the irrigation solution alone, thus providing a potential nonoperative intervention to improve nasal sinus irrigation, which may ultimately enhance topical drug delivery and improve disease management.²²

SINUSURF'S EFFECT ON IRRIGATION BOTTLE CONTAMINATION AND *IN VITRO* EFFICACY OF ANTIBIOTICS

Several studies have shown irrigation bottle bacterial contamination in patients with CRS.^{23,24} Kofonow *et al.* further showed the ineffectiveness of newly described "one-way valve bottles," which were developed to reduce backflow of saline contaminated with nasal bacteria into the main irrigation bottle reservoir.²⁵ In an effort to address bottle contamination, Kofonow examined the role of SinuSurf as a potential bottle cleanser.²⁵ Sinus rinse bottles were inoculated with *P. aeruginosa* or methicillin-resistant *S. aureus* and then flushed daily with either the surfactant solution or the saline. The surfactant solution significantly reduced the CFUs recovered from the residual fluid compared with the saline wash alone, suggesting that surfactants may play a role in reducing nasal irrigation bottle contamination.

In a separate investigational arm of the study by Kofonow *et al.*, the authors investigated the synergistic effects of surfactants and antibiotics (mupirocin and gentamicin).²⁵ In an *in vitro* system of 96-well plates, SinuSurf alone, in the absence of antibiotics, showed a 1000-fold reduction in methicillin-resistant *S. aureus* CFUs and a 10⁶ reduction in *P. aeruginosa*. The addition of surfactant to an antibiotic solution eradicated bacterial growth at a lower antibiotic concentration when compared with the concentrations needed to eradicate growth when using antibiotics alone, suggesting that the addition of surfactants may permit antibiotics to be used at lower concentrations and still achieve similar bacteriocidal results.

CONCLUSION

Surfactants' unique properties make them intriguing as potential adjunctive agents in the treatment of CRS. Although some studies showed clinical efficacy with improved quality of life in recalcitrant CRS patients, other studies question the applicability in the immediate postoperative period. However, the long-term tolerability as well as toxicity profiles must be studied. Further investigation, as well as formula standardization, is warranted to further elucidate the optimal role for surfactants in the treatment of CRS.

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